Taiwan Journal of Ophthalmology 3 (2013) 146–150

Contents lists available at ScienceDirect

Taiwan Journal of Ophthalmology

journal homepage: www.e-tjo.com

Original article

Endogenous candida endophthalmitis in South Taiwan: A 10-year retrospective study

Shih-Hao Wang, Jong-Jer Lee, Yung-Jen Chen, Hsi-Kung Kuo*

Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 21 March 2013
Received in revised form
24 September 2013
Accepted 1 October 2013
Available online 16 November 2013

Keywords:
antifungal
endogenous candida endophthalmitis
visual acuity
vitrectomy

ABSTRACT

Purpose: To investigate the clinical manifestations and the results of the management of endogenous candida endophthalmitis (ECE) at our hospital.
Methods: This study was a retrospective chart review conducted between September 2002 and September 2012.
Results: Our study included 24 eyes of 14 patients. The culture results revealed *Candida albicans* in 11 cases and *Candida tropicalis* in three cases. Diabetes mellitus, cancer, and intravenous catheter implantation were the most important risk factors for ECE. A systemic antifungal agent combined with intravitreal injection or vitrectomy was our method for treating these cases and the complications. The outcomes were generally poor, with a final visual acuity (VA) of better than 0.1 in 10 cases, counting finger to 0.1 in six cases, light perception to hand motion in six cases, and no light perception in two cases.
Conclusion: Unsatisfactory visual outcome in ECE is related to poor initial VA and complications. Early diagnosis and prompt treatment are necessary for these patients.

1. Introduction

Fungal endophthalmitis, which is a vision-threatening condition, may be either exogenous or endogenous. Exogenous infections are usually secondary to trauma or surgery; endogenous fungal endophthalmitis (EFE) represents intraocular dissemination of a systemic fungal infection, and endogenous candida endophthalmitis (ECE) is the most common form of EFE.[1]

Candida species exist as normal flora on the human skin, respiratory tract, gastrointestinal tract, and genitourinary system, and their growth is normally limited by the human immune system. *Candida albicans* is responsible for the majority of candidemia cases among the *Candida* species, but an increasing incidence of infections caused by non-albicans *Candida* species (NAC) has been noted.[2–4] Fungi usually first seed the highly vascular choroid and subsequently move through the retina into the vitreous humor.[5] The occurrence of ECE in patients with candidemia ranges from 9% to 45% in the published literature.[6] Typical presentations of ECE are eye pain, increased floaters, and blurred vision. The risk factors include intravenous drug abuse, hyperalimentation, long-term usage of indwelling catheters, long-term antibiotic treatment, hemodialysis, a recent history of gastrointestinal surgery, and debilitating diseases such as diabetes mellitus or systemic immunosuppression.[5] Rare cases were reported in healthy immunocompetent individuals.[7,8]

The prognosis following ECE depends on the extent of intraocular involvement and the timing and mode of interventions. Some patients have poor visual outcome even after the treatment. Prompt therapy following an early diagnosis helps reduce significant visual loss in ECE. The purpose of our study was to investigate the clinical manifestations and the results of the management of ECE at our hospital.

2. Methods

After obtaining Institutional Review Board (IRB) approval, we retrospectively reviewed the medical records of 14 patients diagnosed with ECE at Kaohsiung Chang Gung Memorial Hospital between September 2002 and September 2012. Patients were eligible if they met both criteria: (1) the typical appearance of ECE such as irregular, fluffy, yellow-white, or gray-white deep retinal lesions, which are frequently accompanied by vitreous haze; and (2) confirmed positivity for candidemia-associated ECE from cultures

The authors have no conflicts of interest relevant to this article.

* Corresponding author. Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Number 123, Ta-Pei Road, Niao-Sung District, Kaohsiung, Taiwan.
E-mail address: oyster@adm.cgmh.org.tw (H.-K. Kuo).

2211-5056/$ – see front matter
http://dx.doi.org/10.1016/j.tjo.2013.10.002

Table 1
Patient characteristics of the study population.

Case no.	Age (y)	Sex	Eye	Initial VA	Associated systemic disease and conditions	Culture result	Systemic treatment	Intravitreal injection of amphotericin B (injection numbers)	Complications or management	Final visual outcome
1	53	M	OD	LP	Type 2 DM Hepatitis B	*Candida albicans*	Fluconazole	Yes (3)	1. RD, PVR grade D2/VT, SB, silicone oil tamponade (OD) 2. Persistent eye pain and no visual function/evisceration (OD)	NLP
			OS	0.05				Yes (2)	No obvious complications during follow-up (OS)	0.3
2	68	M	OS	CF	Heart transplantation Port-A implant	*Candida albicans*	Caspofungin	No	RD with CD/VT, SB, silicone oil tamponade (OS)	HM
3	40	F	OD	0.01	Breast cancer Port-A implant	*Candida albicans*	Amphotericin B	Yes (1)	No obvious complications during follow-up (OD)	0.03
			OS	CF				Yes (2)	RD with CD/VT, SB, gas tamponade (OS)	0.01
4	59	F	OD	0.03	Type 2 DM Recurrent stroke	*Candida albicans*	Fluconazole	Yes (1)	No obvious complications during follow-up (OD)	0.03
			OS	0.01				Yes (2)	Dense epiretinal membrane with tractional RD/VT, silicone oil tamponade (OS)	CF
5	43	F	OD	0.01	Type 2 DM	*Candida albicans*	Fluconazole	No	Macular pucker (OD > OS)/VT (OU)	0.1
			OS	0.1	Hepatitis C			No		1.0
6	48	F	OD	0.02	Type 2 DM	*Candida albicans*	Amphotericin B Fluconazole	Yes (1)	Macular pucker (OU)/VT, gas tamponade (OD)	0.01
			OS	0.03				No		0.01
7	59	M	OD	CF	Type 2 DM Hepatitis C	*Candida albicans*	Fluconazole	No	No obvious complications during follow-up (OD)	0.1
			OS	CF				Yes (2)	Macular pucker/VT (OS)	HM
8	31	M	OD	0.1	Precursor T-cell lymphoblastic lymphoma	*Candida tropicalis*	Caspofungin Fluconazole	Yes (1)	Macular CNV with hemorrhage (OS > OD)/intravitreal injection of Bevacizumab (Avastin) (OS)	0.2
			OS	0.6	Port-A implant Hepatitis B			No		0.7
9	57	M	OS	CF	Tongue cancer Hepatitis C with liver cirrhosis	Yeast-like (Pathology report: candidiasis)	Fluconazole	No	1. Severe vitritis/VT (OS) 2. Corneal melting and perforation/evisceration (OS)	NLP
10	73	F	OD	CF	Type 2 DM Hepatitis C	*Candida albicans*	Fluconazole	Yes (1)	Severe vitritis and vitreous opacity/VT (OD)	LP
11	78	M	OD	HM	Type 2 DM	*Candida albicans*	Fluconazole Micafungin	No	Persistent vitritis and vitreous opacity/observation (OU)	HM
			OS	CF				No		HM
12	82	M	OS	HM	Intravenous catheter	*Candida albicans*	Anidulafungin	Yes (1)	Corneal and vitreous opacity/observation (OS)	HM
13	45	F	OD	0.4	Breast cancer	*Candida tropicalis*	Fluconazole	No	No obvious complications during follow-up (OU)	0.7
			OS	0.5	Port-A implant		Caspofungin Micafungin Voriconazole	No		0.6
14	60	M	OD	0.5	Type 2 DM Hepatitis B	*Candida tropicalis*	Micafungin Voriconazole	Yes (1)	No obvious complications during follow-up (OU)	0.2
			OS	0.8	AML Intravenous catheter Port-A implant			Yes (1)		0.4

AML = acute myeloid leukemia; CD = choroidal detachment; CF = counting finger; CNV = choroidal neovascularization; DM = diabetic diabetes mellitus; F = female; HM = hand motion; LP = light perception; M = male; NLP = no light perception; OD = right eye; OS = left eye; OU = bilateral eyes; PVR = proliferative vitreoretinopathy; RD = retinal detachment; SB = scleral buckle; VA = visual acuity; VT = vitrectomy.

obtained from the vitreous, blood, urine, or cerebrospinal fluid (CSF). Patients with a history of severe ocular trauma, intraocular inflammation, or intraocular surgery were excluded. The collected information included age, gender, the initial visual acuity (VA) at the time of the ECE attack, systemic disorders, associated risk factors, clinical manifestations, culture results, responses to systemic or local treatment, complications, and the final visual outcome.

3. Results

In our study, 24 eyes of 14 patients aged 31–82 years [mean ± standard deviation (SD), 56.86 ± 14.84 years] were diagnosed with ECE. The participants included eight men and six women (Table 1). Involvement of both or one eye was noted in 10 patients (71.4%) and in four patients (28.6%), respectively. Associated underlying systemic diseases were present as follows: eight patients (57.1%) had type 2 diabetes mellitus, six patients (42.9%) had indwelling intravenous catheters (including port-A implants), five patients (35.7%) had cancer, one patient (7.1%) was undergoing systemic immunosuppressive therapy after heart transplantation, and one patient (7.1%) had chronic hepatitis with liver cirrhosis.

According to the cultures obtained from the blood or vitreous humor, 10 cases (71.4%) involved *C. albicans*, which was the most common pathogen found in our study, followed by three cases (23.1%) that involved *Candida tropicalis*. *C. albicans* were also found in the urine cultures of three patients with urosepsis. We also included one case in our study (Case 9) in which the pathology report of the vitrectomy specimen showed candidiasis and the culture yielded yeast-like pathogens.

All patients received treatment with systemic antifungal agents such as amphotericin B, fluconazole, voriconazole, caspofungin, and micafungin. Auxiliary intravitreal injection of amphotericin B (5 μg/0.1 mL) was given to 13 of 24 eyes (54.2%).

The important complications included retinal detachment, macular pucker, choroidal neovascularization (CNV), persistent vitritis, corneal melting, and corneal perforation. Retinal detachment was found in four eyes (16.7%; Cases 1–4), and this was combined with choroidal detachment in two eyes. In one of the two eyes with combined retinal and choroidal detachment, four-quadrant retinal folds with retinal stiffness and a narrow funnel shape were observed in surgery, resulting in a classification as a grade D2 proliferative vitreoretinopathy (PVR) according to the 1983 Retina Society Terminology Committee (Case 1).[9] All four eyes with retinal detachment were treated with vitrectomy and silicone oil tamponade, and three eyes were also treated with implantation with an encircling scleral buckle. During the postoperative follow-up period, three of four eyes had a well-attached retina and the final visual outcomes were hand motion, counting fingers, and 0.01.

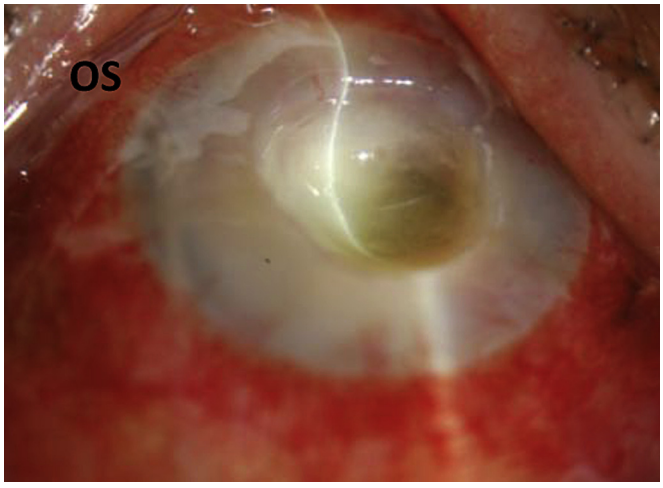

Fig. 2. Case 9. Severe inflammation with total corneal opacity, corneal melting, perforation, and severe conjunctival congestion are apparent in the patient's left eye (OS).

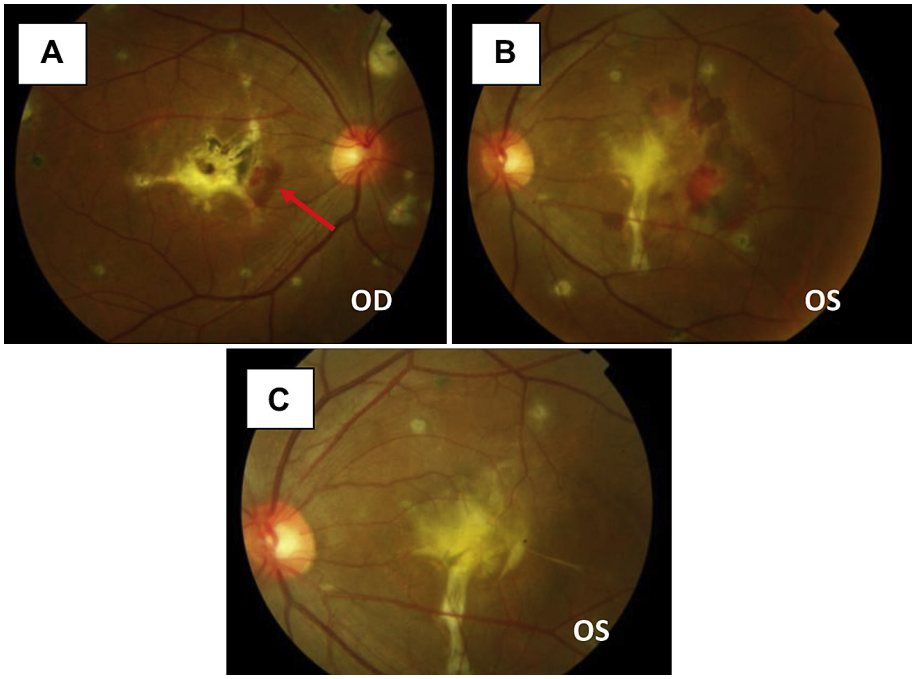

Fig. 1. Case 8. (A) Macular fibrosis and subretinal hemorrhage (arrow) at the nasal side of the parafoveal area are apparent in the right eye (OD). (B) Mild macular fibrosis and massive subretinal hemorrhage at the temporal side of the fovea are apparent in the left eye (OS). (C) In the left eye (OS), the subretinal hemorrhage disappeared after two intravitreal bevacizumab injections during the 4th month of follow-up.

However, the patient with severe PVR eventually lost vision and underwent evisceration because of persistent eye pain.

During the follow-up period, macular pucker occurred in five eyes (20.8%), four of which underwent vitrectomy and epiretinal membrane peeling (Cases 5–7). Among these cases, the final vision in one eye was 1.0 (Case 5), whereas the final vision in others ranged between hand motion and 0.1. Macular CNV and macular hemorrhage occurred in both eyes of one patient 16 months after regression of ECE (Case 8; Fig. 1A and B). He received two intravitreal injections of Bevacizumab (Avastin; 1.25 mg/0.05 mL) in his left eye because of foveal involvement. The CNV of his left eye regressed after the treatment (Fig. 1C). The final VA of his left eye was 0.7, but the VA of his right eye was 0.2 because of macular fibrosis.

Among the 24 eyes included in this study, the final VA was better than 0.1 in 10 eyes (41.7%), counting finger to 0.1 in six cases (25.0%), light perception to hand motion in six cases (25.0%), and no light perception in two cases (8.3%). The two eyes with a final VA of no light perception underwent evisceration because of persistent eye pain in one case (Case 1) and persistent severe inflammation associated with corneal melting and perforation in the other case (Case 9; Fig. 2).

In our study, all of the seven eyes with an initial VA better than 0.1 had a final VA better than 0.1 (100%). By contrast, only three of 17 eyes (17.6%) with an initial VA worse than 0.1 had a final VA better than 0.1. ($p = 0.0003$). Besides, four eyes (Cases 1–4) that were complicated with retinal detachment underwent surgery for treatment, but a final VA better than 0.1 could not be achieved in any eye. However, this association was not significant when compared to the eyes without retinal detachment ($p = 0.1140$).

4. Discussion

In our study, *C. albicans* (76.9%) was the *Candida* species that most frequently caused ECE, followed by *C. tropicalis* (23.1%). These results are similar to those of the study of Essman et al,[10] who identified 17 (85%) *Candida* species and three (15%) *Aspergillus* species in 20 culture-proven EFE cases; in the *Candida* species group, 12/17 (70.6%) cases were *C. albicans* and 5/17 (29.4%) cases were *C. tropicalis*. A notable finding in our study was that the patients infected by *C. tropicalis* all had better visual outcomes than those infected by *C. albicans*, suggesting that *C. tropicalis* is less virulent than the *C. albicans* sp. that causes endogenous endophthalmitis. However, further large randomized controlled clinical trials are required to determine the morbidity and toxicity of these pathogens.

Diabetes mellitus (57.1%) was the most common ECE risk factor, followed by long-term usage of indwelling catheters and cancer. In a study performed by Takebayashi et al[11] in Japan, 43 of 58 patients (74.1%) with EFE had cancer and only one case had diabetes mellitus, which was significantly different from the finding in our study. These variations may result from differences in dietary habits and ethnicity between Taiwanese and Japanese participants as well as the limited number of cases. The study performed by Essman et al[10] showed that long-term intravenous catheter use (67%) was the major predisposing factor of EFE, and most of the patients had more than two risk factors.

We initially used systemic antifungal agents, such as fluconazole or amphotericin B, to treat candida chorioretinitis in our cases. According to the guideline from the Infectious Diseases Society of America (IDSA) in 2009, fluconazole (a loading dose of 800 mg (12 mg/kg), followed by 400 mg (6 mg/kg) daily) or an echinocandin (such as caspofungin, micafungin, or anidulafungin) is recommended as the initial therapy for most non-neutropenic patients with candidemia. However, amphotericin B deoxycholate (0.5–1.0 mg/kg daily) or a lipid formulation of amphotericin B (3–5 mg/kg daily) is an alternative if intolerance or limited availability of other antifungals is an issue. For cases complicated with ECE, amphotericin B (0.7–1 mg/kg) with flucytosine (25 mg/kg, 4 times a day) or fluconazole (6–12 mg/kg daily) is recommended.[12]

An intravitreal injection of amphotericin B was administered if active vitreous inflammation, macular involvement, or evidence that the patient was refractory to current medical therapy was observed. We used a dosage of 5 μg/0.1 mL of amphotericin B for intravitreal injection because previous studies demonstrated that this dose is generally well tolerated.[13] In addition, the intravitreal injection of voriconazole can be used as a newer treatment option in fungal endophthalmitis. Chang et al[14] reported a case with bilateral ECE successfully treated with multiple intravitreal injections of voriconazole combined with systemic treatment. Intravitreal injections of voriconazole (100 μg/0.1 mL) were administered immediately upon the diagnosis of ECE, 3 days after the diagnosis when the systemic condition had stabilized, and as weekly injections for 6 weeks thereafter. The retinal lesions showed regression and the VA improved.

Vitrectomy was considered if the patient had a poor response to the above treatments. However, the effect of vitrectomy remains controversial, and this procedure may be difficult to perform in an infected eye. Takebayashi et al[11] recommended vitreous surgery if medical treatments were ineffective. They reported that 29 eyes of 21 patients who received vitreous surgery still had unsatisfactory visual prognoses, with 16 of 29 eyes (55.2%) having a final vision of less than 0.1 and six eyes (20.7%) having no light perception after the surgery. The poor visual prognosis was probably because the cases were so severe that medical treatment had little effect or was associated with severe complications such as retinal detachment, which independently leads to worse vision. However, in the study performed by Essman et al,[10] only three of 11 patients (27.2%) with *C. albicans*-associated EFE had a final VA of less than 0.1 after receiving vitreous surgery. In our study, 10 eyes received vitrectomy, including four with retinal detachment, four with macular pucker, and two with severe vitritis and persistent vitreous opacities. The final vision was worse than 0.1 in nine eyes (9/10, 90%). The differences among these studies may be associated with the variations in patient selection, surgical indications, and timing.

Tanaka et al[15] divided EFE into four stages: Stage I, chorioretinal changes without extension into the vitreous cavity; Stage II, a fungal mass penetrating through the inner limiting membrane and budding into the vitreous cavity; Stage III, vitreous opacity resulting in a blurred fundus; and Stage IV, Stage III plus the complications of retinal detachment. Takebayashi et al,[11] who described the association between the severity of EFE and the interval between the presence of ocular symptoms and the ophthalmologist's initial visit, found that those with an interval of more than 15 days had a higher rate of occurrence of Stage III or Stage IV EFE at the initial visit. The rate at which patients developed advanced-stage EFE increased as the interval prior to the EFE diagnosis increased, and this association was statistically significant. He also described the association between the severity of EFE and visual prognosis, and reported that all patients with an initial Stage I EFE had a final VA better than 0.1 and 40% were better than 0.6. However, six eyes with initial Stage IV EFE had no light perception.[11]

Poor visual outcome was also related to poor initial VA and centrally located fungal lesions in Sallam's study.[16] These authors included 44 eyes from 36 patients diagnosed with ECE and found that a poor initial VA and a central retinal lesion were the most important risk factors leading to visual loss (VA < 0.5) and severe visual loss (VA < 0.1). Therefore, a satisfactory visual outcome requires an early diagnosis and prompt treatment when indicated. In our study, we also found that 100% eyes with an initial VA better

than 0.1 had a final VA better than 0.1, and only 17.6% eyes with an initial VA worse than 0.1 had a final VA better than 0.1 ($p = 0.0003$). We observed a tendency for the eyes with a better initial VA to have a better visual outcome in general, possibly, because they were diagnosed at an early stage and were able to undergo prompt treatment to prevent the occurrence of associated complications. Moreover, the possible influencing factors leading to poor final visual outcomes were usually related to ECE-associated complications, especially retinal detachment. However, this association was not significant ($p = 0.1140$) because the number of cases was too small.

Macular CNV is usually caused by inflammatory or infectious diseases of the posterior segment. Ocular candidiasis-induced macular CNV was first reported in 1987.[17] Treatment modalities that have been studied for macular CNV include laser photocoagulation, photodynamic therapy, the use of anti-vascular endothelial growth factor (VEGF) agents, and surgical intervention to remove the neovascular membrane.[18–20] Currently, anti-VEGF agents are commonly used because their use is supported by many large randomized studies for the treatment of conditions such as wet-type age-related macular degeneration, diabetic macular edema, or retinopathy of prematurity.[21–23] Furthermore, studies have demonstrated that the use of anti-VEGF agents for the treatment of macular CNV secondary to infectious or inflammatory disorders such as myopic CNV,[24] presumed ocular histoplasmosis syndrome (POHS),[25] Vogt–Koyanagi–Harada (VKH) disease,[26] and uveitic CNV[27] can stabilize the disease and improve the VA. In our study, we also used intravitreal injection of anti-VEGF for macular CNV, which resulted in favorable visual outcome.

The major limitations of our study were the small sample size and the retrospective review of medical records, which limited our ability to study the various factors that may have influenced the visual outcome. In addition, the timing and mode of treatment slightly differed according to the physician, leading to varied results.

In summary, we found that some patients with ECE had unsatisfactory visual outcome even after treatment. The most important risk factors included diabetes mellitus, cancer, and intravenous catheter implantation, and a poor initial VA was an important influencing factor for final outcome. Early diagnosis and prompt treatment are necessary for these patients in order to provide better final vision.

References

1. Marangon FB, Miller D, Giaconi JA, Alfonso EC. *In vitro* investigation of voriconazole susceptibility for keratitis and endophthalmitis fungal pathogens. *Am J Ophthalmol* 2004;**37**:820–5.
2. Chen YC, Chang SC, Luh KT, Hsieh WC. Stable susceptibility of *Candida* blood isolates to fluconazole despite increasing use during the past 10 years. *J Antimicrob Chemother* 2003;**52**:71–7.
3. Kibbler CC, Seaton S, Barnes RA, Gransden WR, Holliman RE, Johnson EM, et al. Management and outcome of bloodstream infections due to *Candida* species in England and Wales. *J Hosp Infect* 2003;**54**:18–24.
4. Pfaller MA, Diekema DJ, Messer SA, Boyken L, Hollis RJ. Activities of fluconazole and voriconazole against 1,586 recent clinical isolates of *Candida* species determined by broth microdilution, disk diffusion and Etest methods: repost from the ARTEMIS global antifungal susceptibility program. *J Clin Microbiol* 2001;**2003**(41):1440–6.
5. Griffin JR, Pettit TH, Fishman LS, Foos RY. Blood-borne candida endophthalmitis: a clinical and pathologic study of 21 cases. *Arch Ophthalmol* 1973;**89**:450–6.
6. Sallam A, Lynn W, McCluskey P, Lightman S. Endogenous candida endophthalmitis. *Expert Rev Anti Infect Ther* 2006;**4**:675–85.
7. Kostick DA, Foster RE, Lowder CY, Meyers SM, McHenry MC. Endogenous endophthalmitis caused by *Candida albicans* in a healthy woman. *Am J Ophthalmol* 1992;**113**:593–5.
8. Valluri S, Moorthy RS, Liggett PE, Rao NA. Endogenous *Aspergillus* endophthalmitis in an immunocompetent individual. *Int Ophthalmol* 1993;**17**:131–5.
9. The classification of retinal detachment with proliferative vitreoretinopathy. *Ophthalmology* 1983;**90**(2):121–5.
10. Essman TF, Flynn Jr HW, Smiddy WE, Brod RD, Murray TG, Davis JL, et al. Treatment outcome in a 10-year study of endogenous fungal endophthalmitis. *Ophthalmic Surg Lasers* 1997;**28**:185–94.
11. Takebayashi H, Mizota A, Tanaka M. Relation between stage of endogenous fungal endophthalmitis and prognosis. *Graefe's Arch Clin Exp Ophthalmol* 2006;**244**:816–20.
12. Pappas PG, Kauffman CA, Andes D, Benjamin Jr DK, Calandra TF, Edwards Jr JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**48**:503–35.
13. Stern GA, Fetkenhour CL, O'Grady RB. Intravitreal amphotericin B treatment of candida endophthalmitis. *Arch Ophthalmol* 1977;**95**:89–93.
14. Chang YF, Yang CS, Lee FL, Lee SM. Voriconazole injection for candida endophthalmitis. *Ophthalmology* 2012;**119**:2414–5.
15. Tanaka M, Kobayashi Y, Takebayashi H, Kiyokawa M, Qiu H. Analysis of predisposing clinical and laboratory findings for the development of endogenous fungal endophthalmitis. A retrospective 12-year study of 79 eyes of 46 patients. *Retina* 2001;**21**:203–9.
16. Sallam A, Taylor SR, Khan A, McCluskey P, Lynn WA, Manku K, et al. Factors determining visual outcome in endogenous candida endophthalmitis. *Retina* 2012;**32**:1129–34.
17. Beebe WE, Kirkland C, Price J. A subretinal neovascular membrane as a complication of endogenous candida endophthalmitis. *Ann Ophthalmol* 1987;**19**:207–9.
18. Recchia FM, Shah GK, Eagle RC, Sivalingam A, Fischer DH. Visual and anatomical outcome following submacular surgery for choroidal neovascularization secondary to candida endophthalmitis. *Retina* 2002;**22**:323–9.
19. Shah GK, Fischer D, Fineman MS, Sharma S, Maguire J. Subretinal neovascularization secondary to candida endophthalmitis: long-term follow-up after submacular surgery. *Retina* 1999;**19**:81–2.
20. Jampol LM, Sung J, Walker JD, Folk JC, Townsend-Pico WA, Lowder CY, et al. Choroidal neovascularization secondary to candida albicans chorioretinitis. *Am J Ophthalmol* 1996;**121**:643–9.
21. Beshshur ZF, Haddad ZA, Schakal A, Jaafar RF, Saab M, Noureddin BN. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: a one-year prospective study. *Am J Ophthalmol* 2008;**145**:249–56.
22. Yilmaz T, Cordero-Coma M, Gallagher M, Teasley LA. Systematic review of intravitral bevacizumab injection for treatment of primary diabetic macular oedema. *Acta Ophthalmol* 2011;**89**:709–17.
23. Mintz-Hittner HA, Kennedy KA, Chunag AZ. Efficacy of intravitreal Bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011;**364**:603–15. http://www.nejm.org/toc/nejm/364/7/.
24. Baba T, Kubota-Taniai M, Kitahashi M, Okada K, Mitamura Y, Yamamoto S. Two-year comparison of photodynamic therapy and intravitreal bevacizumab for treatment of myopic choroidal neovascularisation. *Br J Ophthalmol* 2010;**94**:864–70.
25. Cionni DA, Lewis SA, Petersen MR, Foster RE, Riemann CD, Sisk RA, et al. Analysis of outcomes for intravitreal bevacizumab in the treatment of choroidal neovascularization secondary to ocular histoplasmosis. *Ophthalmology* 2012;**119**:327–32.
26. Wu L, Evans T, Saravia M, Schlaen A, Couto C. Intravitreal bevacizumab for choroidal neovascularization secondary to Vogt-Koyanagi–Harada syndrome. *Jpn J Ophthalmol* 2009;**53**:57–60.
27. Priyanka P, Bhat P, Sayed R, Foster CS. Intravitreal bevacizumab for uveitic choroidal neovascularization. *Ocul Immunol Inflamm* 2009;**17**:118–26.